REMARKS

Applicants have carefully reviewed and considered the Office Action mailed on September 3, 2004 and the documents cited therewith.

In view of the Requirement for Restriction, the Examiner has withdrawn claims 30-42 from consideration. Dependent claims 50-52 have been added. As a result, claims 1-7, 9-15, and 17-52 are pending. Applicant now is paying for one additional independent claim, because the application filing forms inadvertently misstated that one less than the actual number of independent claims were present in the application.

Support for claims 50-52 is found in original claims 3, 11, and 19.

Claims 2, 3, 5, 9-11, 13, 17-19, 21, 27, and 29 have been amended. Claims 8 and 16 have been cancelled.

Claims 3, 11, and 19 have been amended to remove the phrase *such as* from the claims.

Claims 3 and 11 have been amended to recite respectively that the inhibitor of hypoxia-inducible factor 1 alpha ubiquitination or the activator of VEGF transcription consists of a peptide of formula II.

Claims 2, 9, 10, 17, and 18 have been amended to delete SEQ ID NO:5.

Inadvertent typographical errors have been corrected in claims 5, 13, and 21.

Claims 27 and 29 were amended to indicate that the pharmaceutical formulation is administered in conjunction with a wound dressing and a surgical implant, respectively. Support for the amendment is found throughout the specification as filed, for example, at page3, line 23 of Applicants' specification.

The amendments to the specification were made to correct inadvertent typographical errors or to explain abbreviations.

Applicants submit that these changes have added no new matter to the application.

The Examiner again has not referred to the status of claims 43-49 in the Office Action or on the Office Action Summary, Form PTOL-326. Applicants again submit that these claims appear to be part of Group II and therefore also stand withdrawn. Clarification is requested.

Objections to the Specification and Claim 11

Applicants have amended the specification and claim 11 in response to the Examiner's objections that certain abbreviations should be defined at the first occurrence thereof. Furthermore, an additional sequence identifier has been placed immediately after the sequence at page 25, line 30, but it should be noted that *SEQ ID NO: 7* already appears at page 25, line 28 with respect to the sequence at line 30. Finally, *% wt* at page 23, line 25 has been changed to *wt %* to be consistent with the units appearing in the remainder of the paragraph.

Requirement for Restriction

Applicants again traverse the restriction requirement mailed May 26, 2004. The pharmaceutical formulation claims 19-29 are linking claims, pursuant to MPEP § 809.03. These claims link product claims 1-19 and method claims 20-49. Evidence that claims 19-29 are linking claims is the common U.S. patent classification for the pharmaceutical formulation claims and the method claims, namely class 424, subclass 278.1.

Linking claims must be examined with the invention elected, and should any linking claim be allowed, the restriction requirement must be withdrawn. MPEP § 809. The Examiner's restriction requirement and explanation of rejoinder practice are improper in that they do not take the linking claims into account. The Examiner has indicated that rejoinder will be effected only when product claims are elected and a product claim is subsequently found allowable.

In addition, the common U.S. patent classification is further evidence that a serious search burden does not exist. As noted by the Examiner in the restriction requirement, he must search class 424, subclass 278.1 when examining the pharmaceutical formulation claims. As such, he will be perforce searching the method of use claims simultaneously when he notes the intended use of any document that discloses a pharmaceutical formulation. Accordingly, reconsideration and withdrawal of the restriction requirement are respectfully requested.

§101 Rejection of the Claims

Claims 1-18 were rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The Examiner has required evidence of the "hand of

man" in the claims, for example by insertion of the words *isolated* or *purified*. Office Action at page 4. This rejection is respectfully traversed.

The fact that the claimed peptides have been sequenced is evidence that the peptides have been taken out of their natural environment and purified to a degree sufficient to permit sequencing. Therefore, no amendment is necessary. Withdrawal of this rejection is respectfully requested.

§112 Rejection of the Claims

1. Rejections under 35 U.S.C. § 112, second paragraph

Claims 3-29 were rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner rejected claims independent claims 3, 11, and 19 and claims dependent upon these independent claims for recitation of the phrase "such as." Applicants have removed the phrase "such as" and the text that followed the phrase, and have made that text the subject matter of new claims 50-52.

The Examiner rejected claims 5, 13, and 21 as awkward for reciting *t-butylalanine* twice. Applicants have corrected this typographical error in the claims and specification (at page 3) by amending the first recitation to read *n-butylalanine*, another example of an aliphatic amino acid.

The Examiner rejected claim 9 because "the claim recitation 'at least 90% identity to SEQ ID NO:4' does not make sense." Office Action at page 4. The Examiner's rationale is that the peptide with this sequence identifier consists of only 8 amino acids residues; thus, with a minimum of one structural alteration, the maximum sequence identity could be 87.5%. This rejection is respectfully traversed.

As disclosed at page 2 of Applicants' specification, the sequences of claim 9, including SEQ ID NO:4, may be part of longer sequences or may be the unaltered sequences themselves: "Desirable peptides have an amino acid sequence comprising SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:7." If a peptide with SEQ ID NO:4 is not altered structurally, it will have 100% sequence identity with SEQ ID NO:4, thereby comporting with the language of claim 9.

The Examiner rejected claims 27 and 29 because a wound dressing and a surgical implant are not pharmaceutical formulations. Applicants have amended these claims to recite that the

pharmaceutical formulations are administered in conjunction with a wound dressing and a surgical implant, respectively.

Withdrawal of these rejections is respectfully requested.

2. Rejection under 35 U.S.C. § 112, first paragraph

Claim 1 was rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner is of the opinion that Applicants were not in possession of variants of the peptide having the sequence of SEQ ID NO:7 because a representative number of variants of SEQ ID NO:7 retaining the activity of the full length polypeptide are allegedly not disclosed. This rejection is respectfully traversed.

The Court of Appeals for the Federal Circuit recently (October 7, 2004) remanded a case to the Board involving written description support for a genus when only one or more species is disclosed. *Bilstad v. Wakalopulos*, Appeal No. 03-1528. A copy of this decision is provided for the Examiner's convenience. Page numbers cited below are those of the printout from the CAFC website.

The *Bilstad* court acknowledged that the CCPA in *In re Rasmussen*, 650 F.2d 1212, 1215 (CCPA 1981) had recognized that disclosure of a single species within a genus may be sufficient support for a claim to the genus. *Ibid* at 13. In addition, the *Bilstad* court held that the Office must consider the knowledge of persons skilled in the art and the predictability or unpredictability of the art when making a determination of possession of the claimed subject matter at the time of filing. *Ibid* at 16.

The Examiner's statement that Applicants were not in possession of variants of the peptide having the sequence of SEQ ID NO:7 is conclusory and is unsupported by any analysis of the knowledge of persons skilled in the art and the level of predictability of the art. Applicants submit that the knowledge of persons skilled in this art is high, and the predictability in this art is also high. Accordingly, given the disclosed peptide of SEQ ID NO: 7, one would

recognize that Applicants were also in possession of active variants of the peptide of SEQ ID NO:7.

Withdrawal of this rejection is respectfully requested.

§102 Rejection of the Claims

Claims 3-8 and 11-16 were rejected under 35 USC § 102(a) as allegedly being anticipated by Jaakkola et al. (Science, 292, pgs. 468-472, 2001). The Examiner relies upon Figure 3 of Jaakkola et al. for disclosure of the sequence DLDLEMLAPYIPMD, wherein the first proline is hydroxylated. This rejection is respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ 2d 1913, 1920 (Fed. Cir. 1989). To constitute anticipation, the claimed subject matter must be identically disclosed in the prior art. *In re Arkley*, 172 U.S.P.Q. 524 at 526 (C.C.P.A. 1972). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991). To overcome the defense of anticipation, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar Engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172, (9th Cir. 1981).

Initially, Applicants respectfully request clarification of the rejection of claim 6. Claim 6 does not contain a recitation of proline, and proline is an apolar amino acid. Second, the Examiner has not indicated whether the rejection applies to Formula I, to Formula II, or to both.

The subject matter of Formula I has been cancelled from rejected claims 3 and 11. In addition, SEQ ID NO:5 has been deleted from claims 2, 9, 10, 17, and 18. Formula II in the rejected claims, as amended, is not anticipated by Jaakkola et al. Formula II is currently directed to an octapeptide. Jaakkola et al. discloses a synthesized 19 amino acid peptide, residues 556 to 574 of HIF-1α, with the sequence DLDLEMLAPYIPMD-DDFQL wherein the proline at

position 564 is hydroxylated. Accordingly, the claimed invention of Formula II is not identically disclosed by Jaakkola et al.; therefore there can be no anticipation.

Withdrawal of this rejection is respectfully requested.

§103 Rejection of the Claims

Claims 3-10, 11-16, 19-24 and 27-29 were rejected under 35 USC § 103(a) as allegedly being unpatentable over McKnight S.I. et al. (U.S. Patent No. 6,566,088) taken with Jyu et al. (Proc. Natl. Acad. Sci. USA, 98, pgs. 9630-9635, 2001) and Jones et al. (Clin. Cancer Res., 7, pgs. 1263-1272, 2001).

For the record it appears that the first author of the Proc. Natl. Acad. Sci. USA document is Fang Yu. Therefore, the document will be referred to as Yu et al., and not Jyu et al., hereinbelow. The Examiner has cited McKnight et al. for the disclosure of "substrates comprise the peptide LAPY," at column 3, lines 39-41 and similarly at claim 4. The Examiner stated that the McKnight et al. disclosure "reads on" Formula II of Applicants' claim 3. Office Action at page 8. However, at the top of page 9 of the Office Action, the Examiner stated that "McKnight et al. do not expressly teach the sequence which meets all the limitation [sic] set forth in claim 3 formula II."

To remedy this deficiency, the Examiner cited Yu et al. for its teaching of hydroxylation of proline 564 in the sequence disclosed in Figure 2, Panel A.

This rejection is respectfully traversed. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings so as to arrive at the claimed combination. Second, the art must provide a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations (MPEP § 2143). The teaching or suggestion to arrive at the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure (MPEP § 2143, citing with favor *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991)).

First, the combination of McKnight et al. and Yu et al. does not teach or suggest all the claim elements and does not result in Applicants' invention without employing impermissible

hindsight. A disclosure of a peptide *comprising* 4 or 5 amino acids does not render obvious Applicants' octapeptide of Formula II because nothing in the cited documents provides a teaching or suggestion for choosing those amino acids of Applicants' octapeptide that lie outside of the peptide having 4 or 5 amino acids. Further, the Examiner has not set forth reasons for rejecting the pharmaceutical formulation claims 19-24 and 27-29, including where in the documents there is a disclosure of a pharmaceutically acceptable carrier.

Second, there is no motivation to arrive at Applicants' invention from the combination of McKnight et al. and Yu et al. The Examiner has provided no basis in the cited documents for his conclusion that "the skilled artisan would have made an inhibitor of HIF-1α ubiquitination comprising a peptide having the sequence as characterized in Formula II and successfully arrive [sic] at the current invention ...." Office Action at page 9. In fact, there is no motivation in the cited documents to choose 3 or 4 specific amino acids to add to the 4 or 5 of McKnight et al. and then to stop once the 4 or 5 have been added. Such motivation arises only from Applicants' disclosure.

Finally, there is no expectation of success. The combination of documents cited by the Examiner is merely an invitation to experiment. No guidance to arrive at Applicants' invention exists, except Applicants' own disclosure. Withdrawal of this rejection is respectfully requested.

Conclusion

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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By their Representatives,

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Date December 30, 2004 By _____
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: MS Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 30 day of.

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